(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 3 , Page No: 442-448
May-June 2023

IJMSCR

Genetic Factors In Breast Cancer

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Breast cancer is a global epidemic affecting millions of people. For over two decades, research has been conducted to identify the genetic factors linked with a higher risk of breast cancer. Over 30 genes have been found to be correlated with this risk, including the high-penetrance genes BRCA1 and BRCA2, uncommon genes for cancer syndromes, and common variations discovered by genome-wide association studies. Individuals carrying these gene variations have substantial relative risks compared to the general population. The familial pattern of the disease and genetic variation appear to be significant factors in determining risk. Recent studies have focused on understanding the role of widespread genetic variation in the development of breast cancer. Although efforts continue to identify more genetic markers, the significance of these genes in familial breast cancer risk is still not fully understood. This review summarises the current knowledge and data on the genetics of breast cancer and highlights ongoing attempts to uncover additional genetic diversity and its potential therapeutic applications.

Keywords: Breast cancer, BRCA, Epithelial-Mesenchymal Transitions, genome-wide association studies

Introduction

More than 30 genes are among the genetic variables correlated with a higher chance of acquiring breast cancer [(1)]. These include uncommon genes with more moderate penetrance as well as the BRCA1 and BRCA2 high-penetrance for early breast cancer genes, several rare genes for cancer syndrome, and uncommon genes (2). Genome-wide association studies have more recently discovered a bigger group of common variations (3). It is clear from the disease's familial pattern that genetic variation plays a significant role in determining risk (3, 4).

For more than 20 years, extensive research has focused on identifying the genetic variables connected to breast cancer propensity (5). The BRCA1 and BRCA2 linkage maps using family data related to breast cancer was a notable early advance in the genetic analysis of the illness (2, 6). Compared to 3% for the general population, carriers with an uncommon changes to these genes face substantial relative risks that are 10 to 20 times higher, or a 30%–60% risk by the age of 60 (2, 7). The general population's family risk of breast cancer is caused by these mutations, which accounts for 16%–20% of the total risk. Additionally, there are a several uncommon to extremely rare high-penetrance gene variations and a few unusual genes with more moderate penetrance that contribute to cancer syndromes (2, 8). Recent research has centered on how widespread genetic variation functions, through analysis of significant numbers of patients and controls who underwent association testing at tens of thousands of single nucleotide polymorphism (SNP) markers (9, 10). These studies have determined several prevalent breast cancer genes and revealed new insights into the development of the illness (9, 10). Nevertheless, these genes all have low heritability variations and thus only contribute a small portion of the familial

risk (9, 10). This review highlights ongoing efforts to uncover more genetic variation as it examines the evidence's therapeutic application while examining what is understood about the genetics of breast cancer at this time.

Molecular subtypes of breast cancer

An article on molecular subtypes of breast cancer appeared in Nature in 2000. Peru and colleagues divided breast cancer into three subtypes (1) luminal-like (2) Erb-B2^{+} (HER2-enriched), and (3) basal-like (11). According to the gene expression model in human mammary tumor molecular portrait (11).

1. Luminal-like tumors are the most common tumor. accounted for 60%-70% of all tumors. They can be identified by the robust genetic expression of numerous other genes, including the estrogen receptor. epithelial cells aligned at the duct lobular unit (TDLU),where most breast cancer develops; they frequently do not have a significant expression of the transforming gene Erb-B2 (HER2) (11, 12).

2. HER2-enriched tumors account for 12%–20% of all breast cancers. expressed as a quality moderate ER expression was seen with overexpression of the Erb-B2 gene (11, 13).

3. Basal-like tumors comprise approximately 15% of all breast cancer cases and several similar genes identified in cells were expressed (11). They frequently lack the capacity to express ER and many of the genes linked to ER expression in the myoepithelial cells supporting TDLU (11, 14).

Luminal subtypes

The defining feature of the luminal subtype is ER expression. The name “luminal” refers to the genes that are expressed similarly by these tumors and the luminal epithelial cells of the breast (11). The majority of luminal cancers have ER, progesterone receptor (PR), and other genes linked to ER activation genetic expression (15). The luminal subtype of breast cancer, which is the most prevalent subtype, is divided into at least two separate subgroups, A and B (16). Luminal A tumors are more prevalent than luminal B tumors, accounting for about 40% of all breast cancer cases (16). Both the clinical prognosis and gene expression patterns differ significantly between luminal A and B breast cancers (16).

Genetic expression of hormone receptors (HR) is a characteristic of both luminal A and B tumors (17). However, luminal B tumors differ from the luminal A subtype due to a lower expression of PR and a higher expression of proliferative and/or cell-cycle genes (17).Two immunohistochemistry (IHC) markers of cell proliferation, Ki-67 and proliferating cell nuclear antigen, are highly expressed in luminal B cancers but not luminal A tumors (18). Contrary to luminal A cancers, luminal B tumors have a high frequency of p53 mutations (18). In terms of morphology, Endocrine, ductal, mucinous, and classic lobular carcinomas are all examples of well-differentiated malignancies known as luminal A tumors (18). Less differentiated and typically higher graded Luminal B cancers are more aggressive (11, 18).

HER2 enriched (ErbB2) subtype

The transmembrane receptor tyrosine kinase is encoded by the human epidermal growth factor receptor 2 (HER2), which is also known as HER2/neu and Erb-B2. that communicate with extracellular signals to start a cascade that controls cell division, differentiation, and survival. Amplification and/or overexpression of the HER2 gene are present in between 12% and 20% of all breast cancers, which results in rapid tumor growth and a bad prognosis (13). Well-known breast cancer prognostic factors include the HER2 oncogene, which is linked to shorter disease-free survival (DFS) and overall survival (OS) (19). HER2-enriched molecular subtype found to express low levels of ER genes (20). Interestingly, the HER2-enriched subtype does not exhibit the upregulation of proliferation genes like Ki-67 and proliferating cell nuclear antigen (20). Despite this, HER2-enriched tumors still carry worse prognostic than luminal subtypes (21).

Basal-like subtype

Many breast cancer genes are reported to be expressed by either basal or luminal cells, two different types of epithelial cells that can be present in human mammary tissue (13). The "basal-like breast cancer" (BLBC) subtype's (keratin 5, keratin 17, integrin-B4, laminin, and a high expression of genes associated with proliferation) expression features are specific to basal epithelial cells (22). The p53 gene is mutated in the majority of BLBC cancers. Most of the other co-expressed genes as well

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as ER are absent from these malignancies. About 15% of all invasive breast cancers are tumor-like characteristics. Good rates of local and distant recurrence are present, and the tumor is frequently big and of high quality at the time of diagnosis (16, 23).The basal-like subtype predominates in what is known as triple negative breast cancer (TNBC) , which accounts for 70%–80% of all TNBCs .TNBCs and tumors that are triple-negative for breast cancer are diverse groups of diseases. Based on GEP, it is possible to categorize the remaining 20%–30% into at least six different subtypes (e.g., basal-like 1, basal-like 2, immunomodulatory, luminal androgen and mesenchymal stem-like subtypes) (14, 16). TNBC is by definition devoid of ER, PR, and HER2 IHC expression. If less than 1% of a tumor's nuclei express ER and PR as indicated by IHC and are either 0 to 1+by IHC 2+ expression and FISH negative, and IHC for HER2, the tumor is categorized as TNBC (14). ER-, PR-, and HER2 are the most often used IHC surrogates for BLBC. Most TNBCs are ductal carcinomas not otherwise characterized from a morphological perspective Although adenoid cystic, secretory, metaplastic, and medullary carcinomas are all distinct forms of TNBC (19). The IHC phenotype of TNBC, like all intrinsic subtypes, is not the same as the molecular genotype of BLBC, and continuing research demonstrates that TNBCs can be divided into several subtypes, as shown above (18). Additionally, the basal-like group of breast cancer is the most differentiated of the four intrinsic subtypes. It is believed that a widespread luminal progenitor cell line gives rise to breast cancer tumors (18). According to Prat et al, The mammary gland has two quite different types of cell genesis. BLBC is brought on by one, while non-basal breast diseases are brought on by the other (18).

Mendelian high penetrance genes

Approximately 100 genes causing hereditary illnesses with Mendelian family inheritance patterns are recognized (24). These genes are generally uncommon and carry significant relative risks (16). The genetic screening of high-risk families for the spectrum of significant mutations in these genes is well-established (16). The majority of genes have been found by linkage analysis and positional cloning of carefully selected families (16). The breast cancer BRCA1 and BRCA2 genes, which have over a thousand mutations, fall within this group. The BRCA1 'breast cancer 1 early-onset' gene is associated with early-onset breast and ovarian cancer susceptibility, and cancers can occur from somatic or germline alterations (8). In the DNA damage response, BRCA1 acts as a caretaker or master regulator in the genome (8). Impaired or absent BRCA1 activity underpins extensive genomic instability, including increases in the number of mutations, DNA breaks and chromatid exchanges, heightened susceptibility to DNA damage, and dysfunctional cell-cycle checkpoint activities (8).

BRCA2 gene as a crucial modulator of homologous recombination (6). It is a critical component of the DNA repair process, which, if mutated, can result in chromosomal instability and cancer (6). It is known to facilitate recombinational DNA repair by boosting RAD51 assembly on single-stranded DNA (6). This facilitates the invasion and exchange of homologous DNA sequences (25). Errors in the repair process and chromosomal instability may result from mutations in the BRCA2 gene (6). BRCA1 and BRCA2 are likely the only significant breast cancer genes with substantial penetrance (26, 27). Extremely uncommon mutations in the TP53 gene generate the Li–Fraumeni syndrome, a phenotype that includes early-onset breast cancer. Linkage mapping in families, an effective technique for finding numerous Mendelian disease genes, was used to identify both BRCA1 and BRCA2 (2, 27). However, this approach has made little contribution to the research of more prevalent or "complex" types of illness caused by genetic variations with lower penetrance that may interact with environmental and other genetic variables (6). The intricacy of this inheritance pattern considerably lowers the ability of family-based research to find genes (2, 6).

Epithelial-Mesenchymal Transitions Driving Cell-State Heterogeneity

Along a range, cells shift from a developed epithelial state defined by cell-cell adhesion and immobility to a mesenchymal state characterized by motility and invasiveness (28). This continuum of reversible states is traversed by cells, which frequently undergo incomplete EMT in which both epithelial and mesenchymal characteristics are present (28, 29). The hypothesis of reversibility and incomplete EMT reconcile the finding that metastatic tumor cells mostly exhibit an epithelial phenotype devoid of

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apparent mesenchymal transitional characteristics (28, 30). Significantly, EMT signatures have been related to particular subtypes of breast cancer (i.e., claudin-low, basal) and breast cancer stem cell plasticity (31). The elevated EMT signatures associated with the basal and claudin-low subtypes may partially explain the aggressive character of these subtypes since the enhanced motility and invasiveness of a mesenchymal state might contribute to this aggressive phenotype (9, 25). In addition, it is believed that flexibility between EMT and MET phases in response to particular stimuli contributes to the observed heterogeneity in TNBC and drives metastasis within this subtype (25, 32).

The role of tumor-microenvironmental factors in defining tumor heterogeneity : Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) are a critical component of the tumor microenvironment, encouraging cancer development by generating growth factors, controlling tumor immunology, influencing chemoresistance, and promoting metastasis (32). Targeting CAF-driven ITH by inhibiting pathways such as PDGF-CC and FGF5 is a unique approach for preventing tumor cell plasticity and resistance (13, 22, 32, 33). Roswall et al. discovered that PDGF-CC was preferentially expressed in the basal-like molecular subtype of breast cancers and that paracrine cross-talk between CAFs and cancer cells expressing PDGF-CC defined the molecular subtype of the tumor, either luminal or basal (22). They were subsequently able to sensitize ER tumors to antiestrogen therapy via genetic and pharmacological suppression of PDGF-CC signalling (13, 22). By enhancing hedgehog-mediated elevation of FGF5 expression and fibrillar collagen, another study indicated that CAFs provide a supportive habitat for chemoresistant CSCs (13, 22). Inhibiting CAFs in patient-derived xenografts decreased the CSC phenotype and restored docetaxel sensitivity (13, 32).

It has also been demonstrated that heterogeneity across CAFs leads to a treatment-resistant phenotype. Four classes of CAFs are variably related to diverse breast cancer molecular subtypes, with CAF-S1 and CAF-S4 being more prevalent in TNBC (13). It is stated that the CAF-S1 subtype induces an immunosuppressive environment by upregulating CD25HighFOXP3High (Foxhead Box P3) T cells and augmenting T regulatory (Treg) capability (13, 32). According to new research, eight distinct clusters have been identified within the previously recognized CAF-S1 class (13). Researchers established the existence of a positive feedback loop between different clusters and Treg cells, which drives immunoresistance inside these clusters (32). Su et al. found that a CD10+GPR77+ (G protein-coupled receptor 77) subpopulation of cancer-associated fibroblasts (CAFs) maintained cancer stemness and increased resistance to cytotoxic treatment (34). Through antibody-targeted suppression of GPR77 signalling, in vivo docetaxel sensitivity was restored (34). The heterogeneity of cancer-associated fibroblasts (CAFs) and their relation to tumoral resistance is an interesting topic for future research (32, 34).

Clinical uses of breast cancer genetic risk factors

Rare mutations in the BRCA1 and BRCA2 genes are the cause of severe and early-onset variants of breast cancer (6). Screening for these mutations in women with a strong family history can identify individual risks for early-onset breast cancer (35). However, the majority of patients do not have a documented family history of early-onset or late-onset breast cancer (35). The relevance of more common variants of breast cancer in risk prediction is not as well established (10). Studies have shown that common harmful mutations can add a significant risk to the population lifetime risk of breast cancer, which may warrant early and more comprehensive screening for common genetic variants of the disease (25, 36).

As the understanding of the genetic basis of breast cancer continues to grow, we can expect to see continued refinement of genetic risk models (3). One area where refinement may occur is the distinct genetic basis of tumor subtypes. For example, it is well-established that women with ER+ cancer or a greater risk for ER+ cancer are good candidates for therapy with tamoxifen or raloxifene (18). Implementing common breast cancer gene profiles in clinical practice could lead to earlier detection, lower expenses, less intensive therapeutic intervention, and better long-term disease management (8, 37).

Conclusion

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The classification of breast cancer into four intrinsic molecular subtypes has marked a new era in breast cancer research and has led to a shift in therapeutic therapy. While breast cancer remains a feared diagnosis for all women, tailored therapies are helping women with breast cancer to live longer and avoid harsh treatments that often lead to comorbidities. Additionally, each subtype has unique imaging properties and breast imaging continues to play a crucial role in early detection. According to studies, tumor size, nodal status, and intrinsic subtype are the three most important prognostic markers for early breast cancer. Recognizing these four intrinsic molecular subtypes of breast cancer - luminal A, luminal B, HER2-enriched, and basal-like - has begun to unravel the complexity of breast cancer and will lead to the development of additional targeted treatments, thereby improving the prognosis for all women with breast cancer.

Despite extensive research conducted so far, around 70% of the hereditary aspect of breast cancer remains unknown. The common, low-penetrance polymorphisms found by genome-wide association studies (GWAS) have only contributed a small portion of this missing heritability. Except for uncommon mutations in the BRCA1 and BRCA2 genes and a few other rare genes that exhibit Mendelian-like patterns of inheritance, the majority of breast cancer genes discovered do not contribute to the prediction of individual disease risk. A comprehensive understanding of the biological function of the identified variations is still lacking and requires more in-depth functional and bioinformatic study for further advancement.

Studying breast cancer exomes to find SNPs and insertion-deletion polymorphisms will yield valuable insights by offering the first opportunity to explore uncommon types of variation in coding areas. This technique will be efficient for variations with high penetrance, but the interpretation of the functions of multiple uncommon variants may bring additional challenges for bioinformatic and functional assays when penetrance is low. Once these issues are resolved, exome and whole genome sequencing technologies will have the potential to find additional breast cancer genetic risk factors. The discovery of these genes is the essential first step towards a comprehensive understanding of the biology of the disease and the development of personalized therapeutics.

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